UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/879,572	06/12/2001	Arlene I. Ramsingh	29025.0001	4742

30827 7590 01/11/2006

MCKENNA LONG & ALDRIDGE LLP
1900 K STREET, NW
WASHINGTON, DC 20006

EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/879,572	RAMSINGH ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-15,17-22,24-28,30-36 and 54-78* is/are pending in the application.

4a) Of the above claim(s) *2,19 and 54-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6-15,17,18,20-22,24-28,30-36 and 73-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed October 25, 2005 is acknowledged and entered. Also acknowledged are the declarations and accompanying documents filed on May 26, 2005. Claims 1-3, 6-15, 17-22, 24-28, 30-36 and 54-78 are pending. Claims 2, 19 and 54-72 remain withdrawn from consideration, being drawn to non-elected subject matter.

2. Claims 1, 3, 18 and 20-22 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant attenuated coxsackievirus B4 virion (or nucleic acid encoding said virion) which is engineered to contain a heterologous nucleic acid inserted within the P1 region of its genome, wherein the inserted nucleic acid encodes a heterologous polypeptide which is fused to a capsid protein of the virion, does not reasonably provide enablement for an insertion within any region of the open reading frame of its genome. In view of Applicant's amendment to the claims specifying the region in which the heterologous nucleic acid is inserted, the rejection is withdrawn.

The rejection of claims 13-15 and 28 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of Applicant's persuasive remarks further clarifying the claim language.

Claim Rejections - 35 USC § 112

3. Claims 3, 6-15, 17, 20-22, 24-28, 30-36 and 76-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It is apparent that coxsackievirus CB4-P is required to practice the claimed invention because they are a necessary limitation for the success of the invention as stated in the claims. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of coxsackievirus CB4-P. See 37 CFR 1.802. One cannot practice the claimed invention without the specifically named CB4-P coxsackievirus strain. Therefore, access to coxsackievirus CB4-P is required to practice the invention. While the specification provides a method for obtaining a virus that is like CB4-P, the specification does not provide a repeatable method for obtaining *the* CB4-P without access to *the* CB4-P and it does not appear to be readily available material.

Deposit of coxsackievirus CB4-P in a recognized deposit facility would satisfy the enablement requirements of 35 U.S.C. 112., because the strain would be readily available to the public to practice the invention claimed, see 37 CFR 1.801- 37 CFR 1.809. In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the third declaration of Arlene I. Ramsingh, filed May 26, 2005, and the declaration of Steven Tracy, also filed May 26, 2005, both under 37 C.F.R. 1.132. Each declaration is addressed below.

4. Claims 74-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite the new limitation, "non-coxsackievirus", which is not supported by the specification. While the specification gives examples of epitopes of interest that are not coxsackievirus (page 19), the specification does not exclude coxsackievirus chimerics. The specification defines "heterologous nucleic acid" as "any nucleic acid which is not otherwise naturally present in the genome of the virus at the position at which it is inserted", page 12, lines 30-34. This definition clearly encompasses nucleic acid that is from another virus that is not the exact same virus. Therefore, the claims contain new subject matter not supported by the specification.

Previously, claims 1, 3, 4, 6-15, 17-18, 20-28 and 30-36 were rejected for reciting the term, "non-coxsackievirus", for the same reasons cited above. In response to that rejection, Applicant filed arguments (12/3/04) to rebut the rejection, yet also amended the claims to remove the term, "non-coxsackievirus". Since the term has been reintroduced into the claimed invention (new claims 74-78), the arguments filed 12/3/04 are now addressed.

- Applicant argues that the Office did not cite any precedent supporting its position. Applicant then assumes that the Office is relying on the Board's opinion in *Ex parte Grasselli*, 231 USPQ 393 (Pat. Bd. App. & Inf. 1983) for its position on negative limitations. Applicant argues that in the instant case, the facts, issues and reasoning

in *Grasselli* do not apply to the present claims. Applicant asserts that the rejection is a classic elevation of "form over substance".

- In response to Applicant's arguments, 35 U.S.C. 112, first paragraph, requires that the claims contain subject matter which was has been described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In this case, the term is question has not been adequately described. While the specification gives examples of epitopes of interest that are not coxsackievirus (page 19), the specification does not exclude coxsackievirus chimerics. The specification defines "heterologous nucleic acid" as "any nucleic acid which is not otherwise naturally present in the genome of the virus at the position at which it is inserted", page 12, lines 30-34. This definition clearly encompasses nucleic acid that is from another virus that is not the exact same virus.

- Applicant argues that the specification provides examples of non-coxsackievirus chimerics, such as ovalbumin peptides and HIV peptides. These examples alone are adequate support for a claim directed to viruses with inserted non-coxsackievirus heterologous DNA.

  - In response to Applicant's arguments, the examples of ovalbumin peptides and HIV peptides are adequate support for a claim directed to viruses with inserted DNA of ovalbumin peptides and HIV peptides. It is understood that Applicant asserts that they do not believe that coxsackievirus-coxsackievirus chimerics are

truly heterologous. However, the specification was written in such a way as to encompass such an embodiment, though not specifically claimed. Because Applicant did not specifically disclose the embodiment of coxsackievirus-coxsackievirus chimerics, Applicant may not claim around them. Therefore, the rejection is maintained for reasons of record.

Claim Rejections - 35 USC § 102

5. Claims 1, 3, 6-12, 18, 20-22, 24-27, 30-33 and 73 are rejected under 35 U.S.C. 102(b) are anticipated by Caggana *et al.* (*J. Virol.*, 1993, 67:4797-4803, herein, "Caggana"). The claims are now drawn to a recombinant attenuated coxsackievirus B4 virion which is engineered to contain a heterologous nucleic acid inserted within the P1 region of the open reading frame of its genome, which inserted nucleic acid encodes a heterologous polypeptide which is fused to a capsid protein of the virion. The recombinant attenuated coxsackievirus B4 virion (prior to insertion of nucleic acid) is a CB4-P virion. The capsid region is an immunogenic region of the virion which comprises an epitope (B-cell and/or T-cell epitope). The heterologous polypeptide is situated within VP1 at a position which corresponds to the DE loop (see specification page 53), directly downstream of codon 129 of VP1 coding sequences. In one embodiment, the VP1 codons 130-135 of wildtype CB4-P are deleted, as part of the insertion referred to in claim 1. Also claimed are the nucleic acids encoding the recombinant attenuated coxsackievirus B4 virions with the inserts. The heterologous inserted nucleic acid encodes a T cell and/or B cell epitope. The heterologous inserted nucleic acid encodes a viral polypeptide or a fragment thereof.

The teachings of Caggana are of record. Caggana teaches coxsackievirus CB4-P/CB4-V chimeras, in which an attenuated strain, CB4-P expresses heterologous CB4-V proteins of various types (P1, P2, P3) at various regions of the CB4-P genome, including just downstream from codon 129 of VP1, DE loop (page 4797-4798, "Construction of recombinant viruses"; page 4798, Figure 1; pages 4799-4801, bridging paragraph; and page 4802, second column, first line). The VP1 region encodes capsid, which itself is immunogenic and thus contains epitopes (B-cell and/or T cell). As Applicant is aware, the replacement technology employed by Caggana involves deletion. As such, it is entirely expected that VP1 codons 130-135 of wild type CB4-P are deleted when the corresponding gene from the CB4-V is swapped in. Previously, claims that recited this embodiment were not included in the instant rejection. However, upon further consideration, the claims are not written to convey that *only* codons 130-135 are deleted. Since Caggana swaps VP1 genes, the codons are expected to be deleted and replaced by those of CB4-V.

The claim *language* is encompassed by an embodiment disclosed in Caggana. While the Office recognizes the difference between insertion versus replacement, the claim language, in its broadest reasonable interpretation, reads on various embodiments of "insertion". For example, an insertion (in its broadest sense) can be a deletion/insertion combination. Further, the meaning of the term "heterologous nucleic acid" in claims 1, 18 and all respective dependent claims, is interpreted in light of the specification. The specification defines the following terms on page 12, lines 28-33:

> "The term "heterologous polypeptide" refers to a polypeptide which is not otherwise naturally expressed by the virus. The term "heterologous nucleic acid" refers to any nucleic acid which is not otherwise naturally present in the genome of the virus at the position in which it is inserted."

In view of specification's broad definition, the prior art anticipates claims 1, 3, 6-12, 18, 20-22, 24-27, 30-33 and 73.

Applicant has argued that Caggana's chimerics are not intended to be encompassed by the instant claims because Caggana replaces regions of CB4 viruses with other regions of CB4 viruses. Applicant argues that the replacement of CB4-P genes with CV4-V genes is not a heterologous nucleic acid insertion. While the Office acknowledges that the CB4-P and CB4-V strains of coxsackievirus differ by about five amino acids, they remain structurally distinct strains because they have different amino acid sequences that renders one virulent and the other non-virulent. Even though the virulence is credited to one amino acid residue in the capsid protein of VP1 (Caggana, abstract), the sequences of the two remain different. The VP1 region of CB4-P is not the same as the VP1 region of CB4-V, structurally (amino acid difference) and functionally (virulent, non-virulent). As such, Caggana's chimeric meets the claim limitations of being a CB4 virion with heterologous nucleic acid inserted into an open reading frame that results in fusion to the capsid protein of the virion, wherein heterologous nucleic acid is defined as "not otherwise naturally present in the genome of the virus". In the instant case, the P1 region of CB4-V was not naturally present in the genome of the CB4-P virus. Therefore, the claims are encompassed by Caggana. Further arguments are considered below.

Response to Arguments

Third Declaration of Arlene I. Ramsingh

6. The declaration of Arlene I. Ramsingh, an inventor of the instant invention, filed May 26, 2005 has been considered.

- Point 1: Dr. Ramsingh identifies herself as a co-inventor of the instant application and her intention to further explain the history of the Coxsackieviruses B4.
- Points 2 and 3: The prototypic strain of CB4 is JVB, which has been on deposit at the ATCC since the 1950s and has been sequenced. Dr. Ramsingh's lab sequenced half of the JVB strain genome which is in GenBank, Accession #S39291.
- Point 4: Dr. Ramsingh describes the designation of the CB4-P strain: The JVB strain was renamed CB4-P to stand for the prototype CB4 virus that is not virulent. The virulent CB4 virus is named, CB4-V. Dr. Ramsingh states that CB4-P is JVB (except that the sequences are not identical), and JVB was renamed only to distinguish JVB from CB4-V.
- Point 5: The sequence variations between the JVB and CB4-P strains are explained by the natural random variation/spontaneous mutations that occur when a virus replicates, particularly RNA viruses that utilize RNA-dependent RNA polymerase. Dr. Ramsingh reasons that if one were to compare an original JVC virus with a virus progeny from the ATCC JVC strain, the sequences would not be identical.
    - In response to Point 5, the Office recognizes that changes in viral genomes take place from generation to generation as a result of selective pressures and mistakes in transcription and translation. It is understood that a virus progeny from the original JVC virus would yield a virus that has a sequence that is not identical to the orginal JCV sequence. However, the specific claiming of CB4-P requires CB4-P. One cannot work with the designated strain unless it has been provided. If the claims were drawn to viruses that are defined by features of CB4-P that are desired, such as certain mutations in various places in the genome, there would be

not be a deposit issue. However, because Applicant has claimed the specific virus itself, the virus itself must be made publicly available.

- Point 6A: A comparison of the amino acid sequences of several picornaviruses showed that the P1 region encoding the viral polyprotein was the most divergent. There is 77.9% nucleotide sequence identity between the P1 regions of two distinct serotypes, CB3 and CB4.
- Point 6B: A comparison of the sequences of the P1 regions of the JVB virus reported by Jenkins *et al.* (*J. Gen. Virol.* 1987, 68:1835-1848) and CB4-P reported by Ramsingh *et al.* (*Virus Research*, 1992, 23:281-292), reveal 99.8% nucleotide sequence identity, and 99.6% identity at the amino acid level. Dr. Ramsingh concludes that the CB4P and JVB are essentially the same virus population. The variation between the two viruses was to such a minor degree that no phenotypic changes were observed between the two viruses. It is Dr. Ramsingh's opinion that the two viruses would not be considered heterologous relative to each other due to the expected sequence variation between viruses of the same population.
    - In response to Point 6A and 6B, the amount of sequence identity between the CB4-P and JVB is acknowledged. It is Dr. Ramsingh's opinion that the two viruses would not be considered heterologous, rather, homologous. By naming the JVB virus progeny CB4-P, Dr. Ramsingh differentiates the viruses from CB4-V. There are acknowledged differences between JVB and CB4-P, and the viruses are claimed separately (see claims 2 and 3), indicating that the two viral strains are not the same. While the viruses may be considered homologous, they remain

different in terms of sequence. Regardless, the issue at hand is the CB4-P and CB4-V chimeric of Caggana. It is interesting to note that Dr. Ramsingh distinguishes between CB4-P and CB4-V, going so far as to rename JVC as CB4-P.

- Point 7A: Dr. Ramsingh states that given the prior art of record, one of ordinary skill would be able to make and test the claimed chimeric CB4 viruses. Even the sequence of the CB4-P virus described by Ramsingh *et al.* could by reconstructed by starting with a CB4 virus. However, one of ordinary skill in the art would not need the exact CB4 virus to practice the instantly claimed invention. It would not be necessary to acquire the genetically identical sequence to practice the claimed invention.
- Point 7B: Dr. Ramsingh states that any virus that is a genetic equivalent of CB4-P can be used to practice the instant invention, and that the point of genetic equivalence is important when dealing with RNA viruses. CB4-P is one genetic variant of the JVB strain of CB4.
    - In response to Point 7A and 7B, it is understood that the invention can be practiced with other CB4 viruses other than CB4-P. It is also understood that if one were to obtain CB4-P progeny, the sequences of the progeny are likely to be different from the original CB4-P. Nevertheless, the claims are specifically drawn to CB4-P. Without access to CB4-P, one would not be able to practice the invention as claimed because the claims recite, "CB4-P". Without access to CB4-P, one would not be able to obtain progeny of CB4-P.

- Point 8: The specification teaches insertion of heterologous nucleic acids into the genome using CB4-P as but a convenient example. The salient point for appreciating the scope of the invention is the genetic equivalence and not eh phenotypic equivalence because genetically equivalent viruses can be easily manipulated by those skilled in the field to allow insertions of heterologous nucleic acids. The deposited JVB strain of CB4 (ATCC #VR-1840) is genetically equivalent to CB4-P, and functionally similar/equivalent. Dr. Ramsingh points to the specification on page 14, lines 8-15, which discloses that the JVB virus is expected to perform as an equivalent to CB4-P in the generation and use of the viral vector described.
- Point 9: In conclusion, Dr. Ramsingh states that the CB4 virus is publicly available. Additionally, the sequence of the CB4-P virus is available from GenBank. Given the equivalency of JVC and CB4-P, and the sequence information available from GenBank, the Patent Office's position of inadequate description of the CB4-P virus is fully in error. Further, the requirement for a deposit of CB4-P is unnecessary.
    - In response to Points 8 and 9, it is acknowledged that the JVC strain is likely to perform similarly to the CB4-P virus. While this may be true, the fact remains that Applicant is claiming the CB4-P strain. Arguing that there are functional equivalents available does not compensate for the lack of availability of the claimed strain. Further, information available from GenBank is not irrevocably fixed but is corrected and updated as additional sequence information becomes available. The Genbank accession number may refer to sequences which change

after the application filing date. Therefore, the declaration of Dr. Ramsingh is less than adequate to overcome the rejections of record.

Declaration of Steven Tracy

7. The declaration of Steven Tracy filed May 26, 2005 has been considered and is addressed below:

- Points 1 and 2: These points identify Steven Tracy as an expert in the field of viral biology and molecular virology. Dr. Tracy has read and understands the rejection of the claims over Caggana *et al.* (*J. Virol.*, 1993, 67:4797-4803, "Caggana").
- Point 3: Dr. Tracy discusses concepts of virus variability within strains due to mutations during replication. Dr. Tracy states that these differences do not necessarily result in heterologous viruses.
    - In response to Point 3, the Office recognizes that quasispecies are not considered to be different virus classes. The definition of "heterologous" according to Dr. Tracy is different from that of the specification. In this case, the term "heterologous polypeptide" refers to a polypeptide which is not otherwise naturally expressed by the virus. The term "heterologous nucleic acid" refers to any nucleic acid which is not otherwise naturally present in the genome of the virus at the position in which it is inserted.
- Point 4: JVB is a strain of the CB4 serotype. CB4-P and CB4-V can be considered variants of the JVB strain, particularly homologues, not heterologs. Even though they do

not share 100% sequence identity, CB4-P and CB4-V cannot be viewed as heterologous to one another in terms of viral biology.

- In response to Point 4, the Office acknowledges that the two viruses, CB4-P and CB4-V are homologous to some degree because they are both called CB4 viruses. However, according to the specification's definition of heterologous, CB4-P and CB4-V meet the requirements of the definition of heterologous. Clearly, the viruses are different to some degree, and thus are heterologous according to the specification.

- Point 5 is a summary of the examiner's rejection of the instant claims.
- Point 6: Dr. Tracy states that chimeras of Caggana are merely man-made variants of either strain, any of which might occur given time and correct circumstances. Dr. Tracy calls Caggana's chimerics, intratypic chimerics to denote the fact that one homologous region of a related strain of the same serotype was used to replace the original sequence. The instant claims are drawn to true chimeras that have heterologous sequences such as ovalbumin and HIV peptides. The making of Caggana's chimerics involved removal of a CB4 sequence and re-insertion of another closely related and closely homologous CB4 sequence into that space – a replacement. Caggana's work represents a replacement, not an insertion. An insertion adds to the total nucleotide content.
    - In response to Point 6, the Office recognizes that Dr. Tracy considers true heterologous sequences to be those of non-coxsackieviruses. However, the definition of the specification rules over those of Dr. Tracy. Heterologous, by Applicant's definition, is a polypeptide or nucleic acid that is not naturally present

in the recipient genome. CB4-P and CB4-V contain sequences that are not naturally present in the other.

- Further, while the Office recognizes the difference between insertion versus replacement, the claim language, in its broadest reasonable interpretation, reads on various embodiments of "insertion". For example, an insertion (in its broadest reasonable sense) can be a deletion/insertion combination.

- Point 7: Dr. Tracy states that the CB4 nucleic acid sequence that replaces the original CB4 sequence in the other virus should not be considered heterologous, as long as the replacing sequence is the former sequence's homologue in the donor genome. It is Dr. Tracy's opinion that the examiner's interpretation of "heterologous" makes poor biological sense. Particularly in the case of Caggana, Dr. Tracy categorizes the replacement as homologous, not heterologous.
    - In response to Point 7, Applicant is pointed to the definition in the specification of "heterologous". Applicant's disclosure and definition rules over opinions expressed by experts in the field. While Dr. Tracy believes that Caggana's chimerics are not heterologous, a legal point of view and a legal analysis leads back to the specification. Had the definition of heterologous been written in a more definitive manner, the issues surrounding the term, heterologous, would most likely not exist.
- Points 8 and 9: Dr. Tracy summarizes his points regarding the replacement technology used by Caggana, and the homologous gene replacement as opposed to heterologous insertion taught by the inventors of the instant application. Also reiterated is that the

invention as claimed can be practiced with any CB4 virus, not limited by the exact CB4-P strain.

- In response to Points 8 and 9, it is understood that the invention can be practiced with other CB4 viruses other than CB4-P. It is also understood that if one were to obtain CB4-P progeny, the sequences of the progeny are likely to be different from the original CB4-P. Nevertheless, the claims are specifically drawn to CB4-P. Without access to CB4-P, one would not be able to practice the invention as claimed because the claims recite, "CB4-P". Without access to CB4-P, one would not be able to obtain progeny of CB4-P. Therefore, the declaration of Dr. Tracy is inadequate to overcome the rejections of record.

Declaration of Barbara Weiser

8. The declaration of Barbara Weiser filed May 26, 2005 has been considered and is addressed below:

- Points 1 and 2: These points identify Dr. Weiser as an expert in the field of molecular virology and clinical infectious disease. Dr. Weiser has reviewed the relevant section of the Office action and the patent application, including the claims. Dr. Weiser has specialized knowledge of RNA viruses.
- Point 3: Dr. Weiser's research on HIV-1 sequence variation and quasispecies show that the sequences thereof are highly divergent, yet the quasispecies are not considered to be heterologous to each other.

- Point 4: Dr. Weiser states that she was rather stunned to learn that the Patent Office considered CB4-P and CB4-V variants are heterologous to each other. The degree of homology between the two variants is exceedingly small, and to such a degree that they would not be considered separate viral serotypes or strains or classes or whatever other taxonomic term one chooses. Dr. Weiser believes that the skilled artisan would not consider the two heterologous to each other.
    - In response to Points 3 and 4, it is understood that in the field of virology, quasispecies of viruses are not necessarily categorized as heterologous viruses, merely homologs. In this case however, the "homologs" qualify as heterologous because of the specification's definition of the term "heterologous". Because the differing portions of sequences of CB4-P and CB4-V were not present in the other. This is a fact that cannot be reasoned away. There are differences in the genomes, and Caggana replaced one gene with the other corresponding gene. Caggana's work qualifies as heterologous, as defined by Applicant.
- Point 5: The two variants, CB4-P and CB4-V cannot be considered heterologous because the sequences of the two variants are homologous. The sequences encode the same protein with the same biological function, but with one mutated amino acid. Dr. Weiser states that something that is homologous cannot at the same time be heterologous. It is Dr. Weiser's opinion that the examiner's definition of "heterologous" is strained. In the Caggana reference, CB4 virus nucleic acid has been replaced with the homologous segment from a very closely related virus of the same taxon. Dr. Weiser states that her

reading of the application unequivocally does not include Caggana's type of recombination as "heterologous".

- In response to Point 5, Applicant is again pointed to the definition in the specification of "heterologous". Applicant's disclosure and definition rules over opinions expressed by experts in the field.

- Point 6: Note that there is no Point 6 in the declaration as filed.
- Point 7: Dr. Weiser compares the situation of the CB4-P and CB4-V viruses of Caggana with differences between HIV-1 viruses where defined sequence differences are associated with pathogenicity. Dr. Weiser describes a particular situation where variations in the HIV-1 sequence were so great that a pathogenicity difference was observed. Yet, the mutant was still considered to be a homolog, not a heterologous virus.
  - In response to Point 7, the Office recognizes that HIV viruses of different sequences and even pathogenicity are still considered HIV viruses. The examiner is not disputing what is known in the field of virology, or even coxsackieviruses. The examiner is relying on the definition of heterologous, provided by Applicant.
- Point 8: In this section, Dr. Weiser discusses how sequences from HIV-2 and SIV are considered heterologous to HIV-1. Their sequences vary more than 35% at the nucleotide level and are rightly considered distinct viruses. Different primers are needed to amplify HIV-1, HIV-2 and SIV. Dr. Weiser states that the SHIV model expresses the envelope gene of HIV-1 yet can still infect and replicate in rhesus macaques. The SHIV model virus is a chimeric virus, like the recombinant chimeric coxsackieviruses of Applicant's invention, not like the CB4-P and CB4-V viruses of the Caggana reference.

- Point 9: Dr. Weiser summarizes her remarks by reiterating that the Patent Office has defined "heterologous" polypeptides and nucleic acids in a fundamentally different way than the accepted meanings in the scientific community and from the meaning in the instant patent application.
    - In response to Points 8 and 9, the Office maintains its position that, from a legal point of view, the definition of heterologous provided by Applicant overrides others. Based on Applicant's definition, Caggana's chimeric viruses qualify as heterologous. Again, the Office is not arguing against the nature of homologous viruses. Clearly, CB4-P and CB4-V are both CB4 viruses and are homologous in that way. However, replacing unique sequences from CB4-V or CB4-P into the other constitutes introducing a polypeptide which is not otherwise naturally expressed by the virus. Therefore, the declaration of Dr. Weiser is not adequate to overcome the rejections of record.

Declaration of George F. Vande Woude

9. The declaration of George F. Vande Woude filed May 26, 2005 has been considered and is addressed below:

- Points 1 and 2: These points identify Dr. Woude as an expert in the field of virology, molecular biology and particularly molecular oncology. Dr. Woude has reviewed relevant sections of the patent application and the claims.
- Point 3: Dr. Woude understands that claims are drawn to attenuated coxsackievirus B4 virions engineered to express a foreign/heterologous sequences. A foreign sequence is or

can be derived from a different source, not a coxsackievirus of the same serotype or strain, but a truly different virus, such as HIV.

- Point 4: Dr. Woude does not agree with the analysis by the Patent Office of the Caggana reference. The viral variants, CB4-P and CB4-V are not heterologous, nor are they foreign. They are merely allelic variants.
- Points 5 and 6: It is Dr. Woude's opinion that the two variants are homologs, the converse of heterologs. In Caggana's case, a portion of the nucleic acid of a CB4 virus "replaces" a homologous portion of a nucleic acid of the same length to yield the other variant.
    - In response to Points 3-5, Dr. Woude is defining heterologous according to his definition. The definition that must prevail is the one provided by Applicant. A reasonable interpretation of Applicant's definition leads one of skill to consider Caggana's chimeric viruses as prior art. Heterologous, by Applicant's definition, is a polypeptide or nucleic acid that is not naturally present in the recipient genome. CB4-P and CB4-V contain sequences that are not naturally present in the other. The replacement of those sequences results in a virus that has sequences that are not naturally present in its genome. Therefore, the declaration of Dr. Woude is not persuasive and the rejections of record are maintained.

10. A final argument presented by Applicant deals with the subject of fusion. Applicant does not agree that a fusion between a heterologous polypeptide and a capsid protein takes place in

Caggana's recombinant viruses. Applicant asserts that nothing is fused to anything in Caggana, merely mutant VP1 expression which does not qualify as fusion.

In response to this argument, the instant claims encompass the insertion of a heterologous gene into the P1 region of the open reading frame of a coxsackievirus. The expressed heterologous polypeptide is fused to a capsid protein of the virion. It is expected that the replacement gene of Caggana will be fused to a capsid protein of the virion because the original expressed protein is fused to a capsid protein. Lacking any evidence to the contrary, the replacement protein is expected to be fused to a capsid protein in the same manner as the original protein was fused to a capsid protein. If this is not the case, then Applicant's claims lack essential information that should be included in the claims to enable the expression of a fusion protein.

Conclusion

In closing, the examiner notes that Applicant's representative, Dr. Shmuel (Sandy) Livnat, has chosen to take an unprofessional tone, both in his writing and his manner of speaking with Ms. Chen on the telephone. This will not be tolerated. Despite the complicated prosecution history of the instant application and the frustration experienced by Applicant and no doubt Dr. Livnat, a professional tone would be greatly appreciated. Again, the Office sincerely regrets any inconvenience to Applicant.

No claim is allowed. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more

information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen
January 9, 2006